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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
MITRA, RITA	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/897,188	GREGORY D. JAY	
	Examiner	Art Unit	
	Rita Mitra	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *9-16 and 18-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/2/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

Applicants' response to Restriction Requirement dated March 18, 2004 and election without traverse of Group I, claims 1-8 and 17, filed on March 4, 2002 is acknowledged. Claims 9-16 and 18-25 are withdrawn under 37 C. F. R. 1.142 (b) from further consideration by the Examiner, as being drawn to a non-elected invention. Therefore, claims 1-8 and 17 are pending and are under consideration.

Objection to Specification

Table number 1 and 2 are objected to because the sequence identifier appears at the end of the Table. An amendment by entering the SEQ ID NOs on the top, next to the title of the Table would obviate this objection.

The specification indicates at page 39, lines 6-7... 4 different phenotypical isoforms of MSF from both synovial fibroblasts and chondrocytes (Figs. 2A and 2B). There is no part A and B in Fig. 2, an appropriate correction is requested.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-8 and 17 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. These claims recite a "lubricating polypeptide" which reads on the natural, non-patentable, state of the lubricating polypeptide. The rejection would be obviated by the insertion of language indicating that the lubricating polypeptide was isolated and/or purified, thus being removed from the natural environment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a lubricating polypeptide consisting of SEQ ID NO: 1, having at least one O-linked oligosaccharide moiety; does not reasonably provide enablement for any lubricating polypeptide that comprises an amino acid sequence of a variant or a fragment sequence of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The inventions are drawn to encompass lubricating polypeptide fragments and variants of amino acid sequence as set forth in SEQ ID NO: 1. The specification, however, only discloses

cursory conclusions (see page 2-3, 8, 11), which indicates at page 2 that the amino acid sequence of the protein backbone of a lubricating polypeptide may differ depending on alternative splicing of exons of the human megakaryocyte stimulating factor (MSF) gene. Further at page 11 the specification describes that the boundry lubricant isolated from synovial fluid is an alternatively spliced variant of MSF, which was found to be the composition present in synovial fluid that confers lubricating capabilities to the articular joint, and also states that a recombinantly or chemically-produced lubricating polypeptide contains residues encoded by exons 1, 3 and 6-12 of the MSF gene containing at least exon 6 of MSF is useful to prevent and/or treat osteoarthritic disease (pages 11-12). However, the specification fails to describe the specific structure and function of these spliced variants.

While the specification in pages 22-28, describes the isolation and characterization of a lubricating polypeptide from human synovial fluid there is no disclosure about the biological activities of the claimed variants and fragments. Since the specification fails to provide sufficient guidance on the structure and function of the various spliced variants and fragments, it is necessary to have additional guidance on the identities of variants/fragments to carry out further experimentation to assess their property of lubricating and/or inhibiting adhesion formation. Example 1 describes a tribonectin containing sequences encoded by exons 6-9 of the MSF gene but there are no other working examples of the spliced variants claimed in claims 1-8. Moreover, claims 1-8 are interpreted as polypeptide containing Exon 1, 3, 6-12 (claim 1), polypeptide containing Exon 1, 2, 3, 5-12 (claim 2) polypeptide containing Exon 1-4, 6-12 (claim 3) polypeptide containing Exon 1, 3, 6-12 (claim 4) polypeptide containing Exon 1, 3, 6-12 (claim 5) polypeptide containing Exon 1, 3, 6-12 (claim 6) polypeptide containing Exon 1-4, 6-12 (claim 7) polypeptide containing Exon 1, 2, 3, 6-12 (claim 8), and therefore, it would require undue experimentation for a skilled artisan to make and test a large number of the possible variants.

The nature of the invention is lubricating polypeptide comprising at least one O-linked lubricating moiety. The scope of the claims includes spliced variants and fragments of polypeptide. However the specification does not provide the information on the structure (except for the amino acid sequence of the spliced variants) and function of the claimed variants and fragments. The definition of 'glycosylated' at page 5 does not specifically indicate the sites of

the peptides where carbohydrate moiety is present. Therefore, it requires undue experimentation to find out those sites on the polypeptide molecule where O-glycosylation would have been found to effectively be a "lubricating moiety". Furthermore, the specification indicates at page 8 that centrally located exon 6 of MSF gene encodes an O-glycosylated mucin domain and a polypeptide encoded by exon 6 (nucleotides 631-3453 of SEQ ID NO: 2) provides boundary lubrication of articular cartilage. However, the specification fails to describe or demonstrate whether the variants from exons other than exon 6 are retaining the function of the claimed lubricating polypeptide. Thus for these reasons, it requires undue experimentation to make and use the claimed spliced variants.

In the instant case, the amount of experimentation is enormous. Without any guidance or suggestions a skilled artisan would not be able to predict the structure of a variant/fragment that would demonstrate the same activity as the activity of the full-length protein from where it is derived. The art is unpredictable. The number of spliced variants from the starting sequence might be somewhat predictable, if the active areas of the molecule were known, but more changes than that, are less predictable. The number of exons (out of 12 exons) contained in a spliced variant is unpredictable. The effect on function of this many changes is clearly unpredictable. Finally, these claims are very broad in the sense that many of different polypeptides fall within the scope of the claims. Thus, for the reasons set forth above, undue experimentation is required to make and use the claimed variants.

Based on this analysis, the finding of undue experimentation is mandated.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-8 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and 17 are indefinite because it is not clear whether the sequence identity is to the defined residues or to the complete sequence of SEQ ID NO: 1. It is not clear if claim 1 requires amino acid residues 1-25 and 107-199 of SEQ ID NO: 1. Claim 17 is included in this rejection because it depends on a rejected claim, and does not correct the deficiency of the claim from which it depends upon.

Claims 2 and 17 are indefinite because it is not clear whether the sequence identity is to the defined residues or to the complete sequence of SEQ ID NO: 1. It is not clear if claim 2 requires amino acid residues 1-66 and 157-199 of SEQ ID NO: 1. Claim 17 is included in this rejection because it depends on a rejected claim, and does not correct the deficiency of the claim from which it depends upon.

Claims 3 and 17 are indefinite because it is not clear whether the sequence identity is to the defined residues or to the complete sequence of SEQ ID NO: 1. It is not clear if claim 3 requires amino acid residues 1-66 and 107-156 of SEQ ID NO: 1. Claim 17 is included in this rejection because it depends on a rejected claim, and does not correct the deficiency of the claim from which it depends upon.

Claim 4 is indefinite because it is not clear whether the sequence identity is to the defined residues or to the complete sequence of SEQ ID NO: 1. It is not clear if claim 4 requires amino acid residues 1-25 and 157-199 of SEQ ID NO: 1.

Claim 5 is indefinite because it is not clear whether the sequence identity is to the defined residues or to the complete sequence of SEQ ID NO: 1. It is not clear if claim 5 requires amino acid residues 1-25 of SEQ ID NO: 1.

Claim 6 is indefinite because it is not clear whether the sequence identity is to the defined residues or to the complete sequence of SEQ ID NO: 1. It is not clear if claim 6 requires amino acid residues 107-199 of SEQ ID NO: 1.

Applicant is advised that should claim 5 be found allowable, claim 6 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Applicant is advised that should claim 7 be found allowable, claim 8 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 7 and 8 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 7 and 8 have Exons 1-4, and 6-12, which does not constitute a further limitation from the independent claim 3.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 2 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Flannery et al. (Biochemical and Biophysical Research Communication vol 254, pp535-541, Jan 27, 1999, IDS Ref. CC). Flannery discloses an articular cartilage superficial zone protein (SZP), homologous to megakaryocyte stimulating factor precursor. SZP contains large and small mucin like repeat domains, which occur within a large central region of ~940 amino acids. The mucin like domains are likely to be substituted with O-linked oligosaccharides which would impart lubricating properties to SZP which in part accumulates at the articular cartlage-synovial fluid interface (see abstract, and paragraph 3 in col 1, page 536). The reference describes at page 539, col 1 and Fig. 4 that articular cartilage SZP/MSF-precursor contains large (76-78 repeats) and small (6-8 repeats) mucin-like O-linked oligosachharide-rich repeat domains flanked by cysteine-rich N- and C-terminal domains that are homologous to the somatomedin B and hemopexin domains of vitronectin respectively. Flannery also discloses that during normal metabolism the expression of

SZP may be important for both preventing cell attachment to the articular surface as well as maintaining lubrication properties at the articular cartilage-synovial fluid interface (see col 1-2, page 540). Flannery et al also teach that in pathological (osteoartritic) human articular cartilage SZP mRNA can be expressed as an alternatively spliced variant lacking Exons 4 and 5 which encode a potential heparin binding domain (see abstract and col 1, page 538). Flannery teach a transcript corresponding to amino acids Asp202 -Ile258 located at the start of Exon 6 (see Fig. 1) demonstrating the presence of mRNA lacking Exons 4 and 5 (claims 8); and a transcript containing Exon 5 corresponding to Ser158-Ile258 (see Fig. 1) but lacking Exon 4 (claim 2). Therefore, Flannery's spliced variant lacking Exon 4 is considered for the lubricating polypeptide of claim 2, comprising an amino acid sequence of SEQ ID NO: 1 lacking aa 107-156 (Exon 4, Table 3) and with O-linked oligosachharide; and spliced variant lacking Exon 4 and 5 is considered for the lubricating polypeptide of claim 8, comprising an amino acid sequence of SEQ ID NO: 1 lacking aa 107-199 (Exon 4 and 5, Table 3) and with O-linked oligosachharide. Thus claims 2 and 8 are being anticipated by Flannery et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Flannery et al. (Biochemical and Biophysical Research Communication vol 254, pp535-541, Jan 27, 1999, IDS Ref. CC) taken with Turner et al. (US 6433142 B1, prior filing date August 8, 1989, issued August 13, 2002).

Flannery et al. is applied as cited in the above rejection. Flannery et al. discloses an articular cartilage superficial zone protein (SZP), homologous to megakaryocyte stimulating factor precursor. The referenc teaches SZP/MSF-precursor that contains mucin-like O-linked oligosachharide-rich repeat domains. Flannery et al also teach that in pathological (osteoartritic) human articular cartilage SZP mRNA can be expressed as an alternatively spliced variant lacking Exons 4 and 5(claims 8); and a transcript containing Exon 5 but lacking Exon 4 (claim 2). However, Flannery et al. do not teach any other spliced variants of SEQ ID NO: 1, wherein, i) Exon 2, ii) Exon 5, iii) Exon 2, 4, or iv) Exon 2, 4, 5 were missing as claimed in claims 1, 3, 4, 5, 6 and 7. In view of the fact that the reference teaches a protein with O-linked oligosaccharides, having properties of boundry lubricating and preventing cell attachment to the articular surface, and with alternatively spliced variants, it would have been obvious to and motivated one of ordinary skill in the art to have combined the teachings with those of Turner et al.

Turner et al. (US 6433142) teach human megakaryocyte stimulating factors (MSFS) capable of stimulating the growth and development of colonies of megakaryocytes. The reference teaches MSFs that include active fragments and alternatively spliced sequences derived from the cDNA sequence of the precursor protein encoding urinary meg-CSF (see Fig 1 and col 4, lines 59-67). Turner et al. also teach alternatively spliced variants from the sequences encoding MSF protein {see US'142, col 4, 5, 6 (lines 41-46, lines 63-65), col 11(lines 36-53), col 13(lines 28-35), Example 3 and claim 1}. Turner's MSF spliced variants have i) 100 % sequence identity to SEQ ID NO: 1 (aa 1-25+67-1140) (see sequence alignment result, Gesner et al. US 6433142, Database Issued_Patents_AA) (claims 1, 6); ii) 100 % sequence identity to SEQ ID NO: 1 (aa 1-156+200-1404) (see sequence alignment result 1, Gesner et al. US 6433142, Database Issued_Patents_AA) (claims 3, 7); iii) 100 % sequence identity to SEQ ID NO: 1 (aa 1-

106+200-1404) (see sequence alignment result 1, Gesner et al. US 6433142, Database Issued_Patents_AA) (claim 8); iv) 100 % sequence identity to SEQ ID NO: 1 (aa 1-25+67-106+200-1140) (see sequence alignment result 1, Gesner et al. US 6433142, Database Issued_Patents_AA) (claim 5), it should be noted here that aa 1141-1404 (Exons 7-12) of SEQ ID No: 1 are missing because they were not included in the query sequence; v) 100 % sequence identity to SEQ ID NO: 1 (aa 1-106+157-1140) (see sequence alignment result 1, Gesner et al. US 6433142, Database Issued_Patents_AA) (claim 2), it should be noted here that aa 1141-1404 (Exons 7-12) of SEQ ID No: 1 are missing because they were not included in the query sequence; vi) 100 % sequence identity to SEQ ID NO: 1 (aa 1-25+67-106+157-1140) (see sequence alignment result 1, Gesner et al. US 6433142, Database Issued_Patents_AA) (claim 4), it should be noted here that aa 1141-1404 (Exons 7-12) of SEQ ID No: 1 are missing because they were not included in the query sequence.

However, Turner et al. do not teach a protein or spliced variant that has O-linked oligosaccharides which would impart lubricating properties. In view of the fact that Flannery reference teaches a protein and spliced variants with O-linked oligosaccharides having lubricating property, it would have been obvious to and motivated one of ordinary skill in the art to have combined Fannery's spliced variants with amino acid sequence of Turner to give a product as claimed in:

claims 1 and 6 of instant application, wherein claims direct to a lubricating polypeptide having amino acid sequence of SEQ ID NO: 1, wherein the polypeptide lacks aa 26-66 (or Exon 2 of MSF) of SEQ ID NO: 1;

claims 3 and 7 of instant application, wherein claims direct to lubricating polypeptide having amino acid sequence of SEQ ID NO: 1, wherein the polypeptide lacks aa 157-199 (or Exon 5 of MSF) of SEQ ID NO: 1;

claim 8 of instant application, wherein claim directs to lubricating polypeptide having amino acid sequence of SEQ ID NO: 1, wherein the polypeptide lacks aa 107-199 (or Exons 4 and 5 of MSF) of SEQ ID NO: 1;

claim 5 of instant application, wherein claim directs to lubricating polypeptide having amino acid sequence of SEQ ID NO: 1, wherein the polypeptide lacks aa 26-66 and 107-199 (or Exons 2, 4 and 5 of MSF) of SEQ ID NO: 1;

claim 2 of instant application, wherein claim directs to lubricating polypeptide having amino acid sequence of SEQ ID NO: 1, wherein the polypeptide lacks aa 107-156 (or Exon 4 of MSF) of SEQ ID NO: 1;

claim 4 of instant application, wherein claim directs to lubricating polypeptide having amino acid sequence of SEQ ID NO: 1, wherein the polypeptide lacks aa 26-66 and 107-156 (or Exons 2 and 4 of MSF) of SEQ ID NO: 1.

Thus the combined references would have resulted in the claimed invention, which was *prima facie* obvious to make and use at the time it was made.

Conclusion

No claims are allowable.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rita Mitra whose telephone number is (571) 272-0954. The Examiner can normally be reached from 9:30 a.m. to 6:30 p.m. on weekdays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Jon Weber, can be reached at (571) 272-0925. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette,1096 OG 30 (November 15, 1989). The Fax Center number is (703) 872-9306. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0547.

JON WEBER
SUPERVISORY PATENT EXAMINE

Rita Mitra, Ph.D.
October 14, 2004